PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/043447	23.12.2004	30.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D471/04, C07D471/14, A61K31/437, A61P37/02

Applicant
3M INNOVATIVE PROPERTIES COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/043447

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 26-28

because:

☒ the said international application, or the said claims Nos. 26-28(with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/043447

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-25,29-34
	No:	Claims	

2. Citations and explanations

   see separate sheet

Reference is made to the following documents:

D1: WO 00/76519
D2: WERMUTH ET AL: "The Practise of Medicinal Chemistry" PRACTICE OF MEDICINAL CHEMISTRY, 1996, pages 203-237
D3: WO 03/103584
D4: US 2003/96998
D5: WO 2004/58759
D6: US 6 525 064

Re Item II

The priority appears not to be valid for the part of the claims in which R2 is -X-Y-R4 and Y is -O-.
For this part of the claims the document D5 represents prior art. Consequently, the part not enjoying priority does not involve an inventive step.

Re Item III

Claims 26-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

The International Searching Authority found multiple (groups of) inventions in this international application, the reasons being the following:

The closest state of the art for the present application is represented by D1 relating to imidazo[4,5-c]quinolines and tetrahydro-derivatives thereof as immunomodulators. The immunomodulators of D1 exhibit either a sulfonamide (-$NHSO_2$-) or a sulfamide (-$NHSO_2NH$-) group in the substituent on the ring nitrogen atom (cf. examples and claim 1).
The present claim 1 differs from the sulfonamides of D1 only in that the sulfonamide group in the said substituent is inversely orientated. This feature is common to all compounds according to present claim 1.

The technical problem underlying the present claims is seen in the provision of alternative immunomodulators.

The problem is solved by inverting the orientation of sulfonamide group in the substituent on ring-nitrogen of D1 (cf. examples 1-216).
Alternatively, the skilled person arrives at the present compounds by isosterically replacing one NH-group of the sulfamide group in the substituent on ring-nitrogen of D1 by a CH_2 group (cf. D1, examples 217-231 and D2, page 209).
Either of these modifications is regarded as obvious for the skilled person faced with the above mentioned problem. Therefore, the subject-matter of present claim 1 does not involve an inventive step.

Considering that the present compounds exhibiting the feature X'-$SO_2NR_1R_1$' are obvious from D1, the different groups of compounds according to present claims 1 do not share a common special technical feature as required by Rule 13.2 PCT. Therefore, the present application lacks unity of invention (Rule 13.1 PCT).

The following different inventions can be identified:

I Compounds according to claim 1 in which R_A and R_B independently are substituents.
II Compounds according to claim 1 in which R_A and R_B taken together form a fused aryl ring.
III Compounds according to claim 1 in which R_A and R_B taken together form a fused 5 to 7 membered saturated ring.
IV Compounds according to claim 1 in which R_A and R_B taken together form a fused heteroaryl- or a 5 to 7 membered saturated heterocyclic-ring.

Re Item V

The following considerations relate to the first invention (cf. above, claims 1 (part),2 (part),3, 9 (part), 10, 13-28 (part), 33, 34).

1) The subject-matter of present claims is new (Article 33(2) PCT).

2) The subject-matter of claims 1-3, 9, 10, 13-28, 33 and 34 does not involve an inventive step (Article 33(3) PCT).

The closest state of the art for the first invention is represented by D3 relating to imidazo[4,5-c]pyridines as immunomodulators. The immunomodulators of D3 exhibit either a sulfonamide (-$NHSO_2$-) or a sulfamide (-$NHSO_2NH$-) group in the substituent on the ring nitrogen atom (cf. examples 34-53, 102, 113, 117, 118, and claims 1 and 15).

The present claims 1-3 differ from the sulfonamides of D3 only in that the sulfonamide group in the said substituent is inversely orientated.
The technical problem underlying the present claims is seen in the provision of alternative immunomodulators.

The problem is solved by inverting the orientation of sulfonamide group in the substituent on ring-nitrogen of D3 (cf. examples 34-50).
Alternatively, the skilled person arrives at the present compounds by isosterically replacing one NH-group of the sulfamide group in the substituent on ring-nitrogen of D3 by a CH_2 group (cf. D3, example 51 and D2, page 209).
Both of these modifications are regarded as obvious for the skilled person faced with the above mentioned problem. Therefore, the subject-matter of present claims 1-3 does not involve an inventive step.
The dependent claims, the claims relating to a pharmaceutical composition, the claims relating to the use of the compounds and the claims relating to synthetic precursors of the compounds according to claims 1 to 3 (cf. claims 9, 10, 13-28, 33, 34) would only involve an inventive step if the claims 1 to 3 fulfilled this requirement.

2.1) For the same reasons, the document D6 renders the present claims obvious (cf. passages cited in the International Search Report).

The following considerations relate to the second invention (cf. above, 1(part), 2 (part), 4, 5, 12-28 (part), 29, 30).

1) The subject-matter of present claims is new (Article 33(2) PCT).

2) The subject-matter of claims 1, 2, 4, 5, 12-28, 29 and 30 does not involve an inventive step (Article 33(3) PCT).

The closest state of the art is represented by D1 relating to imidazo[4,5-c]quinolines and tetrahydro-derivatives thereof as immunomodulators. The immunomodulators of D1 exhibit either a sulfonamide (-$NHSO_2$-) or a sulfamide (-$NHSO_2NH$-) group in the substituent on the ring nitrogen atom (cf. examples and claim 1).
The present claims differ from the sulfonamides of D1 only in that the sulfonamide group in the said substituent is inversely orientated.

The technical problem underlying the present claims is seen in the provision of alternative immunomodulators.

The problem is solved by inverting the orientation of sulfonamide group in the substituent on ring-nitrogen of D1 (cf. examples 1-216).
Alternatively, the skilled person arrives at the present compounds by isosterically replacing one NH-group of the sulfamide group in the substituent on ring-nitrogen of D1 by a CH_2 group (cf. D1, examples 217-231 and D2, page 209).
Either of these modifications is regarded as obvious for the skilled person faced with the above mentioned problem. Therefore, the subject-matter of present claims 1, 2, 4, 5, 29 and 30 does not involve an inventive step.

The dependent claims, the claims relating to a pharmaceutical composition, the claims relating to the use of the compounds and the claims relating to synthetic precursors of the compounds according to claims 1, 2, 4, 5, 29 and 30 (cf. claims 12-28) would only involve an inventive step if the said claims fulfilled this requirement.

The following considerations relate to the third invention (cf. above, 1 (part), 2 (part), 6, 12-28 (part)).

1) The subject-matter of present claims is new (Article 33(2) PCT).

2) The subject-matter of claims 1, 2, 6 and 12-28 does not involve an inventive step (Article 33(3) PCT).

The closest state of the art is represented by D1 relating to imidazo[4,5-c]quinolines and tetrahydro-derivatives thereof as immunomodulators. The immunomodulators of D1 exhibit either a sulfonamide (-$NHSO_2$-) or a sulfamide (-$NHSO_2NH$-) group in the substituent on the ring nitrogen atom (cf. examples and claim 1).
The present claims differ from the sulfonamides of D1 only in that the sulfonamide group in the said substituent is inversely orientated.

The technical problem underlying the present claims is seen in the provision of alternative immunomodulators.

The problem is solved by inverting the orientation of sulfonamide group in the substituent on ring-nitrogen of D1 (cf. examples 1-216).
Alternatively, the skilled person arrives at the present compounds by isosterically replacing one NH-group of the sulfamide group in the substituent on ring-nitrogen of D1 by a CH_2 group (cf. D1, examples 217-231 and D2, page 209).
Either of these modifications is regarded as obvious for the skilled person faced with the above mentioned problem. Therefore, the subject-matter of present claims 1, 2 and 6 does not involve an inventive step.

The dependent claims, the claims relating to a pharmaceutical composition, the claims relating to the use of the compounds and the claims relating to synthetic precursors of the compounds according to claims 1, 2 and 6 (cf. claims 12-28) would only involve an inventive step if the said claims 1 fulfilled this requirement.

The following considerations relate to the fourth invention (cf. above, 1 (part), 2 (part), 7, 8, 11, 13-28 (part), 31, 32)

1) The subject-matter of present claims is new (Article 33(2) PCT).

2) The subject-matter of claims 1, 2, 7, 8, 11, 13-28, 31 and 32 does not involve an inventive step (Article 33(3) PCT).

The closest state of the art is represented by D4 relating to imidazo[4,5-c]naphthyridines and tetrahydro-derivatives thereof as immunomodulators. The claim 1 of D4 encompasses compounds in which R1 is alkyl-NR3-SO2-X-R4.

The present claims differ from the compounds of D1 only in that the sulfonamide group in the said substituent is inversely orientated.

The technical problem underlying the present claims is seen in the provision of alternative immunomodulators.

The problem is solved by inverting the orientation of sulfonamide group in the substituent on ring-nitrogen.

This modifications is regarded as obvious for the skilled person faced with the above mentioned problem. Therefore, the subject-matter of present claims 1, 2, 7, 8, 31 and 32 does not involve an inventive step.

The dependent claims, the claims relating to a pharmaceutical composition, the claims relating to the use of the compounds and the claims relating to synthetic precursors of the compounds according to the said claims (cf. claims 13-28) would only involve an inventive step if the claims 1, 2 and 6 fulfilled this requirement.

Remark

The term "non-interfering substituent" used in claim 1 does not satisfy the requirements of Article 6 PCT.
The term is to be seen as a functional feature. Functional features are, however,

allowable only if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to a person skilled in the art and which do not require undue experimentation (cf. Guidelines, II, 5.35).